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FORM PTG-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE 661-50303 TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) US APPLICATION NO (If known, see 37 CFR 15) CONCERNING A FILING UNDER 35 U.S.C. 371 INTERNATIONAL FILING DATE INTERNATIONAL APPLICATION NO. PRIORITY DATE CLAIMED PCT/EP99/03451 20 May 1999 22 May 1998 TITLE OF INVENTION ANTISENSE OLIGONUCLEOTIDES FOR TREATING PROLIFERATING CELLS APPLICANT(S) FOR DO/EO/US Flad, Hans-Dieter; Bohle, Andreas; Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:  $_{1}$   $\mathbf{x}$ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U S C 371. This is an express request to promptly begin national examination procedures (35 U S.C 371(f)). x The US has been elected by the expiration of 19 months from the priority date (PCT Article 31). A copy of the International Application as filed (35 U.S.C. 371(c)(2)) is attached hereto (required only if not communicated by the International Bureau). has been communicated by the International Bureau. is not required, as the application was filed in the United States Receiving Office (RO/US). An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). 7. X Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) are attached hereto (required only if not communicated by the International Bureau). have been communicated by the International Bureau. have not been made; however, the time limit for making such amendments has NOT expired. have not been made and will not be made. An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10 An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). Items 11 to 16 below concern document(s) or information included: An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. A FIRST preliminary amendment. A SECOND or SUBSEQUENT preliminary amendment. A substitute specification. A change of power of attorney and/or address letter. 16. X Other items or information: Amend claims 4-8, 10 and 13 as follows, prior to calculating claim fees and without prejudice: Claim 4, line 1, delete "bis 3" Claim 5, line 1, delete "bis 4" Claim 6, line 1, delete "bis 5" Claim 7, line 1, delete "bis 6" Claim 8, line 1, delete "bis 7" Claim 10, line 1, delete "bis 8" Claim 13, line 1, delete "oder 12". The Claims have been amended to remove multiple dependency only. No claims have been amended to overcome prior art.

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#### PTO RECEIPT FOR INDICATED ITEMS

Transmittal Letter to US Designated Office Concerning Filing Under 35 USC 371

International Application No.: PCT/EP99/03451

Inventor: Flad

Title: Antisense Oligonucleotides for Treating Proliferating Cells

Attorney Docket No.: 661-50303

Preliminary Amendment

Fee Sheet

Check for \$1,120.

The PTO did not receive the following listed item(s)

09/700906

Current Due Date: November 22, 2000

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#### Certification of Translation

I, Heinz-Peter Muth of UEXKÜLL & STOLBERG, Patent Attorneys in Hamburg, Germany, do hereby certify that I am conversant with the English and German languages and am a competent translator thereof, and I further certify that to the best of my knowledge and belief the foregoing is a true and correct translation made by me of the International Application No. PCT/EP99/03451 filed May 20, 1999 into the English language.

Hamburg, January 5, 2001

Heinz-Peter Muth

09/700906 Rec'd PCT/PTO 26 FEB 2001

# Phy

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# Antisense oligonucleotides for treatment of proliferating cells

The invention relates to oligoribo- and oligodeoxyribonucleotides which are suitable for treating pathological conditions accompanied by an increased cell proliferation.

5 Nucleic acid fragments of which the sequence is complementary to the coding or "sense" strand of DNA or a messenger RNA (mRNA) and which are therefore capable of binding specifically to these complementary target sequences (hybridizing) are called antisense oligonucleotides. Selective influencing of cell processes is 10 possible by this means. Antisense oligonucleotides have found interest as tools in research and as potential agents for antiviral and tumour therapy (E. Uhlmann, A. Peyman, Chemical Reviews, 90 (1990) 544-584; S. Agrawal, TIBTECH 10 (1992) 152-158) and in some cases have already reached the stage of clinical research (M.D. Matteucci, R.W. Wagner, Nature 384 (196) 20-22).

Ki-67 is a cell protein which is produced in all active phases of the cell cycle  $(G_1, S, G_2 \text{ and mitosis})$ , but not during the resting phase  $(G_0)$ . The resting or  $G_0$  phase describes the state in which the dividing activity of the cell is at rest, i.e. the cells have left the active phases of the cell cycle and do not divide. Ki-67 is a human nuclear protein, expression of which is associated strictly with cell proliferation. Specific antibodies against the Ki-67 protein are used in histopathology for determination of the proportion of growing cells in human tumours (J. Gerdes, Seminars in Cancer Biology 1 (1990) 199-206).

It has furthermore been found that proliferation of human IM-9 cells can be inhibited as a function of the concentration by a 30 Ki-67 protein antisense 2'-deoxyoligonucleotide comprising 21

bases (C. Schlüter et al., The Journal of Cell Biology, 123 (1993) 513-522). The complete nucleotide sequence of the cDNA of the Ki-67 protein and the derived amino acid sequence are known (Schlüter et al., loc. cit.). Figure 1 (SEQ ID NO 1) shows the sense strand of the Ki-67 cDNA.

The object of the present invention is to provide antisense oligonucleotides which are suitable for treating pathological conditions accompanied by an increased cell proliferation.

10 Examples of such disease states are tumours, allergies, autoimmune diseases, cicatrization, inflammations and rheumatic diseases, as well as suppression of rejection reactions in case of transplantations.

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- 15 This object has been achieved by oligoribo- or oligodeoxyribonucleotides, and physiologically acceptable salts thereof, which are capable of hybridizing with the mRNA which codes for the protein Ki-67.
- 20 Ιt has been found that the oligoribooligodeoxyribonucleotides according to the invention have a cytotoxic and not only inhibiting action on proliferating cells, such as, for example, tumour cells, and cause the death of the cells. This finding is surprising in as much as the Ki-67 25 protein is not detectable in non-proliferating cells and is thus evidently not necessary for survival of the cells.

Oligonucleotides which hybridise with Ki-67 mRNA at  $37^{\circ}\text{C}$  and a physiological saline concentration are preferred.

Oligoribo- and oligodeoxyribonucleotides, and in particular oligodeoxyribonucleotides, of which the sequence is complementary to the nucleotide sequence, shown in figure 1 (SEQ ID NO: 1), of the sense strand of the cDNA of Ki-67, i.e. at a chain length of 10 bases has not more than 0 to 4, preferably 0 to 2, and even more preferably no mismatches, are particularly preferred.

Oligoribo- and oligodeoxyribonucleotides which hybridise with a nucleotide sequence from the 5' region of the Ki-67 mRNA, i.e. oligoribo- or oligodeoxyribonucleotides which are complementary to the 5' region of the sequence shown in figure 1, preferably to a section of the region from position 197 to 2673 or 2673 to 9962, particularly preferably 197 to 220, have furthermore proved to be particularly active.

The oligonucleotides according to the invention preferably have 10 a chain length of 12 to 66 nucleotides, particularly preferably 17 to 46 and very particularly preferably 22 to 46 nucleotides.

The sequence (SEQ ID NO: 3):

15 (5'-ACC AGG CGT CTC GTG GGC CAC AT)

is very particularly preferred.

Non-modified oligonucleotides, and in particular non-modified oligoribonucleotides, are subject to nucleolytic degradation to a high degree and therefore have only a low stability and biological half-life. To improve ability to penetrate through membranes and to increase the biological half-life, the bases, sugar residues and/or phosphate residues of the oligonucleotides according to the invention are preferably modified.

Oligonucleotides in which one or more phosphate groups are replaced by phosphothioate, methylphosphonate, phosphoramidate, methylene(methylimino) (MMI) and/or guanidine groups 30 preferred. The structure of these groups is shown in figure 2. Thiolated oligonucleotides, i.e. oligonucleotides in which phosphate groups are replaced by phosphothioate groups, are particularly preferred. One or more of the phosphate groups of the oligonucleotide can be modified. In the case of partial modification, terminal groups are preferably modified, oligonucleotides in which all the phosphate groups are modified are most preferred.

Preferred sugar modifications comprise replacement of one or more ribose residues of the oligonucleotide by hexose (figure 2) or by amino acids (peptide nucleic acid, PNA, figure 2).

5 Modifications of the bases comprise the use of 5-propinyl-uracyl, 5-propinylcytosine and the tricyclic cytosine analogue phenoxazine.

The synthesis of modified oligonucleotides and further suitable ways of modification are described in the literature (cf., for example, E. Uhlmann, A. Peyman, loc. cit.; M.D. Matteucci, R.W. Wagner, loc. cit.).

The oligonucleotides according to the invention can moreover be protected against degradation by exo-nucleases by terminal 3'-3' and/or 5'-5' internucleotide bonds (H. Seliger et al., Nucleosides & Nucleotides 10 (1-3), 469-477 (1991)).

The oligonucleotides according to the invention can furthermore additionally be substituted by groups which promote intracellular uptake, which serve *in vivo* or *in vitro* as reporter groups, and/or groups which, during hybridization of the oligoribonucleotide on the target RNA, attack the same by bonding or cleavage.

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Examples of groups which promote intracellular uptake are lipophilic residues, such as alkyl residues, for example having 1 to 18 C atoms, cholesteryl or thiocholesteryl groups (E. Uhlmann, A. Peyman, loc. cit.) or conjugates which utilise natural carrier systems, such as e.g. bile acid or peptides for the corresponding receptor (e.g. receptor-mediated endocytosis).

Examples of reporter groups are fluorescent groups (e.g. acridinyl, dansyl or fluorescinyl groups) or chemiluminescent groups, such as e.g. acridinium ester groups.

Examples of oligonucleotide conjugates which bond to and/or cleave nucleic acids are to be found in E. Uhlmann, A. Peyman, loc. cit. Conjugate partners are, inter alia, acridine, psolaren, chloroethylaminoaryl, phenanthridine, azidophenacyl, azidoproflavine, phenazine, phenanthroline/Cu, porphyrin/Fe, benzo[e]pyridoindole and EDTA/Fe (Mergny et al., Science 256 (1992) 1681).

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The oligonucleotides according to the invention are prepared in a manner known per se (cf. e.g. E. Uhlmann, A. Peyman, loc. cit.). Synthesis on a solid phase with the aid of an automatic synthesis apparatus is preferred.

To prepare medicaments, the oligonucleotides according to the invention are combined with conventional carrier substances, auxiliaries and/or additives. The oligonucleotides are suitable for systemic, local, subcutaneous, intrathecal and topical use and for administration by enema. For this, they can be used as a solution in suitable solvents, preferably aqueous solutions, in the form of liposomes, as an emulsion or in solid form, for example as a powder or in microencapsulated form.

The amount of oligonucleotides in the medicaments depends on the desired use and is preferably adjusted such that an administration of 0.001 to 100 mg oligonucleotide per kg of body weight, preferably 0.001 to 10 mg/kg of body weight, particularly preferably 0.01 to 3 mg/kg of body weight is achieved. Treatment is preferably carried out by repeated use over a period of one day to 6 weeks in a dose of preferably 0.01 to 3 mg/kg per day.

The oligonucleotides according to the invention are suitable for treating pathological conditions accompanied by an increased cell proliferation, in particular for treatment of benign and malignant tumours, such as testicular tumours, lymphomas, gastric carcinomas, bladder carcinomas, mammary carcinomas, bronchial carcinomas, sarcomas, renal carcinomas and melanomas, autoimmune

diseases, cicatrization, inflammations, allergies, rheumatic diseases and rejection reactions in case of transplantations.

A particular advantage of the oligonucleotides according to the invention is to be seen in that they allow treatment of tumours which are resistant to conventional chemotherapeutics. Such resistances arise either secondarily, i.e. after several administrations, with non-specific cytostatics, such as, for example, vinblastin or cisplatin, or are already primarily present with certain tumours, such as, for example, renal carcinoma.

The finding that the oligonucleotides according to the invention not only inhibit the growth of cells but also have a cytotoxic action, i.e. lead to the death of the treated tumour cells, was particularly surprising. The cytotoxic action in general starts after a treatment time of about 5 to 12 days. A treatment time of some months may be necessary for complete destruction of all the proliferating cells, whereby the treatment time may be interrupted by periods of non-treatment.

The invention is explained in more detail with the following examples.

#### 25 Example 1

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# Action on the growth of RT4 cells in the multicellular spheroid test

- 30 The action of oligonucleotides according to the invention on bladder carcinoma cells of the cell line RT4 was investigated on multicellular spheroids and compared with corresponding sense and missense strands as a control.
- For this, 2'-deoxyoligonucleotides with the following sequences were prepared in a known manner (Uhlmann and Peyman, loc. cit.):

- 7 -

start-2-anti 5'-ACC AGG CGT CTC GTG GGC CAC AT start-2-sense 5'-ATG TGG CCC ACG AGA CGC CTG GT missense 5'-AGT ACT CAG TAA CGC CTA CGG TAA G

5 Unless stated otherwise, all the oligonucleotides were employed in thiolated form, i.e. one oxygen atom of the phosphoric acid radicals was replaced by a sulphur atom.

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Multicellular spheroids of the cell line RT-4 (ATCC no.: HTB2) were prepared by the method of Carlsson & Yuhas (J. Carlsson and J.M. Yuhas, Liquid-overlay culture of cellular spheroids, Recent Results in Cancer Research 95; 1-23, 1984). After four days the multicellular spheroids showed a spherical morphology with a pronounced, sharp demarcation. The RT4 multicellular spheroids were then incubated in the presence of 120 µmol/l of the particular oligonucleotides in culture media at 37°C with 5% CO2 and the change in the spheroid diameter was measured. oligonucleotides were introduced into the medium directly after the period of time necessary for formation of the spheroids. the one hand a sample to which no oligonucleotides were added (control) and on the other hand the missense oligonucleotide samples served as negative controls. Thereafter, the diameter of the multicellular spheroids was measured at intervals of 2 days. Three identical batches were investigated per test and the mean was then obtained. The results are plotted as a graph in figure 3.

An increase in the spheroid diameter to 132% of the starting value was observed in the control, while the addition of the thiolated missense oligonucleotide caused a stop in growth. The addition of the sense oligodeoxynucleotide caused a slight reduction in the spheroid diameter to 90%, while the antisense oligonucleotide led to a rapid decrease in the spheroid diameter down to complete dissolution of the spheroid on the 12th day of incubation.

After co-incubation of the multicellular spheroids with oligonucleotides, these were furthermore tested in respect of their vitality with the aid of fluorescent dyes. The dyes used for this were fluorescein-labelled disodium acetate (FITC-FDA) and propidium iodide (PI). Each multicellular spheroid was incubated with 2  $\mu$ l FITC-FDA in a concentration of 1  $\mu$ mol/l for 20 minutes and with 10  $\mu$ l PI (concentration: 20  $\mu$ g/ml) for 10 minutes. Under a fluorescence microscope living cells appear green due to the FITC-FDA staining and dead cells appear red due to the PI staining. A pronounced cytotoxic reaction of the cells investigated in the antisense-treated group was found.

The results show that the antisense oligonucleotide according to the invention is cytotoxic to the tumour cell line tested and causes irreversible cell damage, which leads to death of the cell.

To rule out the solvent alone having an influence on growth, corresponding control experiments were carried out with the solvent (solvent; only the solvent of the oligonucleotides, but not the oligonucleotides themselves, was added), which showed that this influencing parameter was to be ignored (cf. figure 4).

#### Example 2

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# Action on the growth of RT4 cells by microinjection

The action of the oligonucleotides mentioned in example 1 on RT4 cells by direct injection of the compounds into the cell was investigated. The oligonucleotides were employed in non-modified (non-thiolated) form for this experiment. By this test, on the one hand the activity of non-modified oligonucleotides is to be demonstrated, and on the other hand non-specific binding of the oligodeoxynucleotides to cell membrane receptors being responsible for the effects described in example 1 is to be ruled out.

RT4 cells were sown on special cover glasses (CELLocate cover glasses, Eppendorf). A grid etched into the centre of these cover glasses facilitates finding the injected cells again. Before the cells were sown the cover glasses were placed in Petri dishes with a diameter of 3.5 cm and wetted with in each case 1  $\mu$ l fibronectin, which ensures better attachment of the cells. 1.5 x  $10^5$  cells, which had been dissolved beforehand by means of trypsin, were then sown per dish in 2.5 ml supplemented RPMI 1640 medium and were cultured at 37°C overnight in an incubating cabinet.

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The microinjection was carried out with the aid of a transjector 5246 and micromanipulator 5171 (Eppendorf) under light microscope control (inverse microscope type Leitz DMIL, Leica). microinjection capillaries were filled with in each case 2.0  $\mu l$ 15 oligonucleotide solution (concentration 120  $\mu mol/l$ ) with the aid of  $Mikroloader^{\mathfrak{p}}$  pipette tips (Eppendorf). The concentration was adjusted with sterile-filtered phosphate-buffered saline solution (PBS). To check the permeability of the filled capillaries, the clean function of the transjector was employed under microscopic 20 With the capillary open, after immersion into the control. culture medium a uniform outflow of injection liquid was observed. The injection pressure was set empirically at 130 hPa and corrected after the first injections such that the injection 25 led to a clear increase in the size of the cell, without destroying it. The injection time was between 0.3 and 0.5second.

For the cytoplasmic injections, the capillary tip was brought up to the cytoplasm until a reflection of light caused by pressure on the cell was to be observed. The capillary was then raised again a few µm and the automatic injection movement was triggered by pressing the button. During the injection the injection limit could be corrected upwards or downwards in 0.14 µm steps, so that irregularities in the cell substrate could be compensated. For comparative studies, microinjection capillaries which were drawn in one working operation were used in order to keep the amount

of liquid flowing out per injection as constant as possible for the same injection parameters. Nevertheless, the volume initiated varied from cell to cell, since the injection pressure and therefore the solution to be injected could spread out to a better or worse degree, depending on the region hit. To minimize the effects of cooling and a pH shift of the culture medium on the growth behaviour of the cells, the total injection time per cell culture dish was limited to 15 minutes.

10 The results of the test are plotted as a graph in fig. 5. It was found that injection of antisense oligonucleotides and a subsequent incubation time of 22 hours resulted in a loss of adhesion in approx. 70% of the cells. Since only living cells remain adhered to the cover glass, this result is to be equated with death of 70% of the cells. Injection of the sense or missense oligonucleotides led only to a loss of adhesion in 30% of the cells in each case, and sole injection of the solvent (PBS) led to a loss of adhesion in 10% of the cells.

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#### Example 3

#### Action on the growth of J82 cells

The action of the oligonucleotides on the human bladder tumour cells line J82 was investigated analogously to example 1. The thiolated antisense oligonucleotide in a concentration of 120 µmol/l led to a decrease in the spheroid diameter by 20% after 11 days, while the spheroid diameter of the control increased by about 30% in the same period of time (fig. 6).

## - 11 -

## SEQUENCE LISTING

_	(1) GENERAL INFORMATION:	
5	<ul> <li>(i) APPLICANT:</li> <li>(A) NAME: Forschungszentrum Borstel</li> <li>(B) STREET: Parkallee 1-40</li> <li>(C) CITY: Borstel</li> </ul>	
10	(D) State: Schleswig-Holstein (E) COUNTRY: Germany (F) POSTAL CODE: D 23845	
15	(ii) TITLE OF INVENTION: Antisense-Oligonucleotides for treating proliferating cells	
	(iii) NUMBER OF SEQUENCES: 3	
20	<pre>(iv) COMPUTER READABLE FORM:     (A) MEDIUM TYPE: Floppy disk     (B) COMPUTER: IBM PC compatible     (C) OPERATING SYSTEM: PC-DOS/MS-DOS     (D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPA)</pre>	
25	(2) INFORMATION FOR SEQ ID NO: 1:	
30	<ul> <li>(i) SEQUENZ CHARACTERISTICS:</li> <li>(A) LENGTH: 12493 base pairs</li> <li>(B) TYPE: Nucleotid</li> <li>(C) STRANDEDNESS: dopple strand</li> <li>(D) TOPOLOGY: linear</li> </ul>	
35	(ii) MOLECULE TYPE: cDNS	
40	(ix) FEATURE: (A) NAME/KEY: CDS (B) LOCATION: 1979964	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:	
4 5	CTACCGGGCG GAGGTGAGCG CGGCGCCGGC TCCTCCTGCG GCGGACTTTG GGTGCGACTT	6
45	GACGAGCGGT GGTTCGACAA GTGGCCTTGC GGGCCGGATC GTCCCAGTGG AAGAGTTGTA	12
	AATTTGCTTC TGGCCTTCCC CTACGGATTA TACCTGGCCT TCCCCTACGG ATTATACTCA	18
50	ACTTACTGTT TAGAAA ATG TGG CCC ACG AGA CGC CTG GTT ACT ATC AAA  Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys  1 5 10	22
55	AGG AGC GGG GTC GAC GGT CCC CAC TTT CCC CTG AGC CTC AGC ACC TGC Arg Ser Gly Val Asp Gly Pro His Phe Pro Leu Ser Leu Ser Thr Cys 15 20 25	27
60	TTG TTT GGA AGG GGT ATT GAA TGT GAC ATC CGT ATC CAG CTT CCT GTT Leu Phe Gly Arg Gly Ile Glu Cys Asp Ile Arg Ile Gln Leu Pro Val 30 35	32
65	GTG TCA AAA CAA CAT TGC AAA GTT GAA ATC CAT GAG CAG GAG GCA ATA Val Ser Lys Gln His Cys Lys Val Glu Ile His Glu Gln Glu Ala Ile 45	37

## - 12 **-**

	TTA Leu 60	His	AAT Asn	TTC Phe	AGT Ser	TCC Ser 65	Thr	AAT Asn	CCA Pro	ACA Thr	CAA Gln 70	ı Val	AAT Asn	GGG Gly	TCT Sei	GTT Val	421
5	ATT Ile	GAT Asp	GAG Glu	CCT Pro	GTA Val 80	. Arg	CTA Leu	AAA Lys	CAT His	GGA Gly 85	Asp	GTA Val	ATA Ile	ACT Thr	AT1 11e	ATT Ile	469
10	GAT Asp	CGT Arg	TCC Ser	TTC Phe 95	Arg	TAT Tyr	GAA Glu	AAT Asn	GAA Glu 100	Ser	CTT Leu	CAG Gln	AAT Asn	GGA Gly 105	Arg	AAG Lys	517
15	TCA Ser	ACT Thr	GAA Glu 110	Phe	CCA Pro	AGA Arg	AAA Lys	ATA Ile 115	CGT Arg	GAA Glu	CAG Gln	GAG Glu	CCA Pro 120	Ala	. CGT . Arg	CGT	565
20	GTC Val	TCA Ser 125	Arg	TCT Ser	AGC Ser	TTC Phe	TCT Ser 130	TCT Ser	GAC Asp	CCT Pro	GAT Asp	GAG Glu 135	AAA Lys	GCT Ala	CAA G1n	GAT Asp	613
_ •	TCC Ser 140	AAG Lys	GCC Ala	TAT Tyr	TCA Ser	AAA Lys 145	ATC Ile	ACT Thr	GAA Glu	GGA Gly	AAA Lys 150	Val	TCA Ser	GGA Gly	AAT Asn	CCT Pro 155	661
25	CAG Gln	GTA Val	CAT His	ATC Ile	AAG Lys 160	Asn	GTC Val	AAA Lys	GAA Glu	GAC Asp 165	AGT Ser	ACC Thr	GCA Ala	GAT Asp	GAC Asp 170	TCA Ser	709
30	AAA Lys	GAC Asp	AGT Ser	GTT Val 175	GCT Ala	CAG Gln	GGA Gly	ACA Thr	ACT Thr 180	AAT Asn	GTT Val	CAT His	TCC Ser	TCA Ser 185	GAA Glu	CAT His	757
35	GCT Ala	GGA Gly	CGT Arg 190	AAT Asn	GGC Gly	AGA Arg	AAT Asn	GCA Ala 195	GCT Ala	GAT Asp	CCC Pro	ATT Ile	TCT Ser 200	GGG Gly	GAT Asp	TTT Phe	805
40	AAA Lys	GAA Glu 205	ATT Ile	TCC Ser	AGC Ser	GTT Val	AAA Lys 210	TTA Leu	GTG Val	AGC Ser	CGT Arg	TAT Tyr 215	GGA Gly	GAA Glu	TTG Leu	AAG Lys	853
10	TCT Ser 220	GTT Val	CCC Pro	ACT Thr	ACA Thr	CAA Gln 225	TG <b>T</b> Cys	CTT Leu	GAC Asp	AAT Asn	AGC Ser 230	AAA Lys	AAA Lys	AAT Asn	GAA Glu	TCT Ser 235	901
45	CCC Pro	TTT Phe	TGG Trp	AAG Lys	CTT Leu 240	TAT Tyr	GAG Glu	TCA Ser	GTG Val	AAG Lys 245	AAA Lys	GAG Glu	TTG Leu	GAT Asp	GTA Val 250	AAA Lys	949
50	TCA Ser	CAA Gln	AAA Lys	GAA Glu 255	AAT Asn	GTC Val	CTA Leu	CAG Gln	TAT Tyr 260	TGT Cys	AGA Arg	AAA Lys	TCT Ser	GGA Gly 265	TTA Leu	CAA Gln	997
55	ACT Thr	GAT Asp	TAC Tyr 270	GCA Ala	ACA Thr	GAG Glu	AAA Lys	GAA Glu 275	AGT Ser	GCT Ala	GAT Asp	GGT Gly	TTA Leu 280	CAG Gln	GGG G1y	GAG Glu	1045
60	ACC Thr	CAA Gln 285	CTG Leu	TTG Leu	GTC Val	TCG Ser	CGT Arg 290	AAG Lys	TCA Ser	AGA Arg	CCA Pro	AAA Lys 295	TCT Ser	GGT Gly	GGG Gly	AGC Ser	1093
30	GGC Gly 300	CAC His	GCT Ala	GTG Val	GCA Ala	GAG Glu 305	CCT Pro	GCT Ala	TCA Ser	CCT Pro	GAA Glu 310	CAA Gln	GAG Glu	CTT Leu	GAC Asp	CAG Gln 315	1141

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											GTT Val						1189
5											CCG Pro						1237
10	CCT Pro	GTA Val	CAA G1n 350	TAT Tyr	TCA Ser	CAG Gln	CAA Gln	CAA Gln 355	AAT Asn	TCT Ser	CCA Pro	CAA Gln	AAA Lys 360	CAT His	AAG Lys	AAC Asn	1285
15											TCT Ser						1333
20											CTT Leu 390						1381
2.0											GAA Glu						1429
25											ACC Thr						1477
30											GAA Glu						1525
35											AGG Arg						1573
40											ACA Thr 470						1621
40											ATC Ile						1669
45											AAA Lys						1717
50											GAT Asp						1765
5 <b>5</b>											ACC Thr						1813
60	GTA Val 540	ATG Met	CAC His	ACT Thr	CCA Pro	CCT Pro 545	GTC Val	CTG Leu	AAG Lys	AAA Lys	ATC Ile 550	ATC Ile	AAG Lys	GAA Glu	CAG Gln	CCT Pro 555	1861
00	CAA Gln	CCA Pro	TCA Ser	GGA Gly	AAA Lys 560	CAA Gln	GAG Glu	TCA Ser	GGT Gly	TCA Ser 565	GAA Glu	ATC Ile	CAT His	GTG Val	GAA Glu 570	GTG Val	1909

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	AAG Lys	GCA Ala	CAA Gln	AGC Ser 575	TTG Leu	GTT Val	ATA Ile	AGC Ser	CCT Pro 580	CCA Pro	GCT Ala	CCT Pro	AGT Ser	CCT Pro 585	Arg	AAA Lys	1957
5	ACT Thr	CCA Pro	GTT Val 590	GCC Ala	AGT Ser	GAT Asp	CAA Gln	CGC Arg 595	CGT Arg	AGG Arg	TCC Ser	TGC Cys	AAA Lys 600	Thr	GCC Ala	CCT Pro	2005
10	GCT Ala	TCC Ser 605	AGC Ser	AGC Ser	AAA Lys	TCT Ser	CAG Gln 610	ACA Thr	GAG Glu	GTT Val	CCT Pro	AAG Lys 615	Arg	GGA G1y	GGA G1y	GAA Glu	2053
15	AGA Arg 620	Val	GCA Ala	ACC Thr	TGC Cys	CTT Leu 625	CAA G1n	AAG Lys	AGA Arg	GTG Val	TCT Ser 630	Ile	AGC Ser	CGA Arg	AGT Ser	CAA Gln 635	2101
20							ATA Ile										2149
	GAA Glu	GCA Ala	AAT Asn	CTG Leu 655	ATT Ile	GTT Val	GCA Ala	AAA Lys	TCA Ser 660	TGG Trp	GCA Ala	GAT Asp	GTA Val	GTA Val 665	AAA Lys	CTT Leu	2197
25	GGT Gly	GCA Ala	AAA Lys 670	CAA Gln	ACA Thr	CAA Gln	ACT Thr	AAA Lys 675	GTC Val	ATA Ile	AAA Lys	CAT His	GGT Gly 680	CCT Pro	CAA Gln	AGG Arg	2245
30							AGA Arg 690										2293
35	GGC Gly 700	GAA Glu	GTT Val	CAC His	AGT Ser	CAA Gln 705	TTT Phe	AGT Ser	ACA Thr	GGC Gly	CAC His 710	GCA Ala	AAC Asn	TCT Ser	CCT Pro	TGT Cys 715	2341
40							GCT Ala										2389
	CGA Arg	CCC Pro	TAC Tyr	AGA Arg 735	GTG Val	CTC Leu	AAC Asn	AAC Asn	TTC Phe 740	ATT Ile	TCC Ser	AAC Asn	CAA Gln	AAA Lys 745	ATG Met	GAC Asp	2437
45							GGA Gly										2485
50							ACA Thr 770										2533
55							AAA Lys										2581
60							TCA Ser										2629
<b>J J</b>							AAA Lys										2677

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						CAG Gln										AAA Lys	2725
5						TAC Tyr										TCA Ser	2773
10						CCT Pro 865											2821
15						TTC Phe											2869
20						AAT Asn											2917
20						CTA Leu											2965
25						TTT Phe											3013
30						ATG Met 945											3061
35						ATG Met											3109
4 0						AAA Lys											3157
40						AAG Lys								Lys			3205
45			Pro			TCA Ser		Gln					Asn				3253
50		Thr				TTG Leu 1025	Lys					Lys					3301
55						GTC Val )					Arg					Thr	3349
60	ACG Thr	CAC His	ACG Thr	CAC His 1055	Arg	GAG Glu	CCA Pro	GCA Ala	GGA Gly 1060	Asp	GGC Gly	AAG Lys	AGC Ser	ATC Ile 1065	Arg	ACG Thr	3397
0.0				Ser		AAG Lys			Leu					Arg			3445

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	GGA Gly	ATG Met 108	Lys	AAG Lys	TGG Trp	CCA Pro	AGA Arg 109	Thr	CCT Pro	AAG Lys	GAA Glu	GAG Glu 109	Ala	CAG Gln	TCA Ser	CTA Leu	3493
5	GAA Glu 110	Asp	CTG Leu	GCT Ala	GGC Gly	TTC Phe 110	Lys	GAG Glu	CTC Leu	TTC Phe	CAG Gln 111	Thr	CCA Pro	GGT Gly	CCC Pro	TCT Ser 1115	3541
10	GAG Glu	GAA Glu	TCA Ser	ATG Met	ACT Thr 112	Asp	GAG Glu	AAA Lys	ACT Thr	ACC Thr 112	Lys	ATA Ile	GCC Ala	TGC Cys	AAA Lys 113	Ser	3589
15	CCA Pro	CCA Pro	CCA Pro	GAA Glu 113	Ser	GTG Val	GAC Asp	ACT Thr	CCA Pro 114	Thr	AGC Ser	ACA Thr	AAG Lys	CAA Gln 114	Trp	CCT Pro	3637
20	AAG Lys	AGA Arg	AGT Ser 115	Leu	AGG Arg	AAA Lys	GCA Ala	GAT Asp 115	Val	GAG Glu	GAA Glu	GAA G1u	TTC Phe 116	Leu	GCA Ala	CTC Leu	3685
20	AGG Arg	AAA Lys 116	Leu	ACA Thr	CCA Pro	TCA Ser	GCA Ala 1170	GGG Gly O	AAA Lys	GCC Ala	ATG Met	CTT Leu 117	Thr	CCC Pro	AAA Lys	CCA Pro	3733
25	GCA Ala 118	Gly	GGT Gly	GAT Asp	GAG Glu	AAA Lys 118	Asp	ATT Ile	AAA Lys	GCA Ala	TTT Phe 119	Met	GGA Gly	ACT Thr	CCA Pro	GTG Val 1195	3781
30	CAG Gln	AAA Lys	CTG Leu	GAC Asp	CTG Leu 1200	Ala	GGA Gly	ACT Thr	TTA Leu	CCT Pro 120	G1y	AGC Ser	AAA Lys	AGA Arg	CAG Gln 121	Leu	3829
35	CAG G1n	ACT Thr	CCT Pro	AAG Lys 121	Glu	AAG Lys	GCC Ala	CAG Gln	GCT Ala 1220	Leu	GAA Glu	GAC Asp	CTG Leu	GCT Ala 1225	G1y	TTT Phe	3877
40	AAA Lys	GAG Glu	CTC Leu 1230	Phe	CAG Gln	ACT Thr	CCT Pro	GGT G1y 1235	His	ACC Thr	GAG Glu	GAA Glu	TTA Leu 1240	Val	GCT Ala	GCT Ala	3925
	GGT Gly	AAA Lys 1245	Thr	ACT Thr	AAA Lys	ATA Ile	CCC Pro 1250	TGC Cys )	GAC Asp	TCT Ser	CCA Pro	CAG Gln 1255	Ser	GAC Asp	CCA Pro	GTG Val	3973
15	GAC Asp 1260	Thr	CCA Pro	ACA Thr	AGC Ser	ACA Thr 1265	Lys	CAA Gln	CGA Arg	CCC Pro	AAG Lys 1270	Arg	AGT Ser	ATC Ile	AGG Arg	AAA Lys 1275	4021
50	GCA Ala	GAT Asp	GTA Val	GAG Glu	GGA Gly 1280	Glu	CTC Leu	TTA Leu	GCG Ala	TGC Cys 1285	Arg	AAT Asn	CTA Leu	ATG Met	CCA Pro 1290	Ser	4069
55	GCA Ala	GGC Gly	AAA Lys	GCC Ala 1295	Met	CAC His	ACG Thr	CCT Pro	AAA Lys 1300	Pro	TCA Ser	GTA Val	GGT Gly	GAA Glu 1305	Glu	AAA Lys	4117
50	GAC Asp	ATC Ile	ATC Ile 1310	Ile	TTT Phe	GTG Val	GGA Gly	ACT Thr 1315	Pro	GTG Val	CAG Gln	AAA Lys	CTG Leu 1320	Asp	CTG Leu	ACA Thr	4165
, 0	GAG Glu	AAC Asn 1325	Leu	ACC Thr	GGC Gly	AGC Ser	AAG Lys 1330	AGA Arg	CGG Arg	CCA Pro	CAA Gln	ACT Thr 1335	Pro	AAG Lys	GAA Glu	GAG Glu	4213

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		Gln				GAC Asp 134	Leu					Glu					4261
5						GAA Glu O					Gly					Met	4309
10	CCC Pro	TGC Cys	GAA Glu	TCT Ser 137	Ser	CCA Pro	CCA Pro	GAA Glu	TCA Ser 1380	Ala	GAC Asp	ACC Thr	CCA Pro	ACA Thr 138	Ser	ACA Thr	4357
15				Pro		ACA Thr			Glu					Gln			4405
20	CTC Leu	TCA Ser 140	Ala	CTG Leu	AAG Lys	AAG Lys	CTC Leu 1410	Thr	CAG Gln	ACA Thr	TCA Ser	GGG Gly 141	Glu	ACC Thr	ACA Thr	CAC His	4453
20		Asp				GGA Gly 1425	Gly					Ile					4501
25						AAA Lys O					Ala					Ser	4549
30	AAG Lys	AGG Arg	CAC His	CCA Pro 1455	Lys	ACT Thr	AAG Lys	GAA Glu	AAG Lys 1460	Ala	CAA Gln	CCC Pro	CTA Leu	GAA Glu 1465	Asp	CTG Leu	4597
35	GCT Ala	GGC Gly	TGG Trp 1470	Lys	GAG Glu	CTC Leu	TTC Phe	CAG Gln 1475	Thr	CCA Pro	GTA Val	TGC Cys	ACT Thr 1480	Asp	AAG Lys	CCC Pro	4645
40			His			ACT Thr		Lys					Ser				4693
<b>T</b> 0	CCA Pro 1500	Val	GAC Asp	ACA Thr	CCA Pro	ACA Thr 1505	Ser	TCC Ser	AAG Lys	CCA Pro	CAG Gln 1510	Ser	AAG Lys	AGA Arg	AGT Ser	CTC Leu 1515	4741
45						GAA Glu )					Ala					Thr	4789
50	CCA Pro	TCA Ser	GCA Ala	GGC Gly 1535	Lys	GCC Ala	ATG Met	CAC His	ACA Thr 1540	Pro	AAA Lys	CCA Pro	GCA Ala	GTA Val 1545	Ser	GGT Gly	4837
55				Ile		GCA Ala			Gly					Lys			4885
c 0			Glu			ACT Thr		Ser					G1n				4933
60		Lys				CTA Leu 1585	Glu					Phe					4981

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	CAG Gln	ACA Thr	CGA Arg	GGT Gly	CAC His 160	Thr	GAG Glu	GAA Glu	TCA Ser	ATG Met 160	Thr	AAC Asn	GAT Asp	AAA Lys	A ACT Thr 161	GCC Ala O	5029
5	AAA Lys	GTA Val	GCC Ala	TGC Cys 161	Lys	TCT Ser	TCA Ser	CAA Gln	CCA Pro 162	Asp	CTA Leu	GAC Asp	AAA Lys	AAC Asr 162	Pro	GCA Ala	5077
10	AGC Ser	TCC Ser	AAG Lys 163	Arg	CGG Arg	CTC Leu	AAG Lys	ACA Thr 163	Ser	CTG Leu	GGG Gly	AAA Lys	GTG Val 164	G1y	GTG Val	AAA Lys	5125
15	GAA Glu	GAG Glu 164	Leu	CTA Leu	GCA Ala	GTT Val	GGC Gly 1650	Lys	CTC Leu	ACA Thr	CAG Gln	ACA Thr 165	Ser	GGA Gly	GAG Glu	ACT Thr	5173
20	ACA Thr 166	His	ACA Thr	CAC His	ACA Thr	GAG Glu 166	Pro	ACA Thr	GGA Gly	GAT Asp	GGT Gly 167	Lys	AGC Ser	ATG Met	AAA Lys	GCA Ala 1675	5221
20	TTT Phe	ATG Met	GAG Glu	TCT Ser	CCA Pro 1680	Lys	CAG G1n	ATC Ile	TTA Leu	GAC Asp 168	Ser	GCA Ala	GCA Ala	AGT Ser	CTA Leu 169	Thr	5269
25	GGC Gly	AGC Ser	AAG Lys	AGG Arg 169	CAG Gln 5	CTG Leu	AGA Arg	ACT Thr	CCT Pro 170	Lys	GGA Gly	AAG Lys	TCT Ser	GAA Glu 170	Va1	CCT Pro	5317
30	GAA Glu	GAC Asp	CTG Leu 171	Ala	GGC Gly	TTC Phe	ATC Ile	GAG Glu 1715	Leu	TTC Phe	CAG Gln	ACA Thr	CCA Pro 172	Ser	CAC His	ACT Thr	5365
35	AAG Lys	GAA Glu 1725	Ser	ATG Met	ACT Thr	AAT Asn	GAA Glu 1730	Lys	ACT Thr	ACC Thr	AAA Lys	GTA Val 173	Ser	TAC Tyr	AGA Arg	GCT Ala	5413
40	TCA Ser 1740	Gln	CCA Pro	GAC Asp	CTA Leu	GTG Val 1745	Asp	ACC Thr	CCA Pro	ACA Thr	AGC Ser 1750	Ser	AAG Lys	CCA Pro	CAG Gln	CCC Pro 1755	5461
40	AAG Lys	AGA Arg	AGT Ser	CTC Leu	AGG Arg 1760	Lys	GCA Ala	GAC Asp	ACT Thr	GAA Glu 1765	Glu	GAA Glu	TTT Phe	TTA Leu	GCA Ala 1770	Phe	5509
45	AGG Arg	AAA Lys	CAA Gln	ACG Thr 1775	CCA Pro	TCA Ser	GCA Ala	GGC Gly	AAA Lys 1780	Ala	ATG Met	CAC His	ACA Thr	CCC Pro 178	Lys	CCA Pro	5557
50	GCA Ala	GTA Val	GGT G1y 1790	GLu	GAG Glu	AAA Lys	GAC Asp	ATC Ile 1795	Asn	ACG Thr	TTT Phe	TTG Leu	GGA Gly 1800	Thr	CCA Pro	GTG Val	5605
55	CAG Gln	AAA Lys 1805	Leu	GAC Asp	CAG Gln	CCA Pro	GGA Gly 1810	Asn	TTA Leu	CCT Pro	GGC Gly	AGC Ser 1815	Asn	AGA Arg	CGG Arg	CTA Leu	5653
6.0	CAA Gln 1820	Thr	CGT Arg	AAG Lys	GAA Glu	AAG Lys 1825	Ala	CAG Gln	GCT Ala	CTA Leu	GAA Glu 1830	G1u	CTG Leu	ACT Thr	GGC Gly	TTC Phe 1835	5701
60	AGA Arg	GAG Glu	CTT Leu	TTC Phe	CAG G1n 1840	Thr	CCA Pro	TGC Cys	Thr	GAT Asp 1845	Asn	CCC Pro	ACA Thr	GCT Ala	GAT Asp 1850	G1u	5749

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·					Lys					Ser					CCA Pro 5		5797
5				Thr					Arg					Leu	AAG Lys		5845
10	GCA Ala	GAC Asp 188	Val	GAG Glu	GAA Glu	GAA G1u	TTT Phe 189	Leu	GCA Ala	TTC Phe	AGG Arg	AAA Lys 189	Leu	ACA Thr	CCA Pro	TCA Ser	5893
15		Gly					Thr					Va1			GAG Glu		5941
20	GAC Asp	ATC Ile	AAC Asn	ACA Thr	TTT Phe 192	Val	GGG Gly	ACT Thr	CCA Pro	GTG Val 192	Glu	AAA Lys	CTG Leu	GAC Asp	CTG Leu 1930	Leu	5989
20					Gly					Pro					GAA Glu 5		6037
25				Leu					G1y					Phe	CAG Gln		6085
30	CCA Pro	GGT Gly 1965	His	ACT Thr	GAG Glu	GAA Glu	TCA Ser 1970	Met	ACC Thr	GAT Asp	GAC Asp	AAA Lys 1975	Ile	ACA Thr	GAA Glu	GTA Val	6133
35		Cys					Pro					Thr			AGC Ser		6181
40						Ile					Val				GAA Glu 2010	G1u	6229
	GTC Val	CTA Leu	CCA Pro	GTC Val 2015	Gly	AAG Lys	CTC Leu	ACA Thr	CAG Gln 2020	Thr	TCA Ser	GGG Gly	AAG Lys	ACC Thr 2025	ACA Thr	CAG Gln	6277
45				Glu					G1y					Ala	TTT Phe		6325
50			Ala					Asp					Gly		GGG Gly		6373
55		Arg					Pro					Gln			GAA Glu		6421
60						Glu					Pro				GAG G1u 2090	Glu	6469
					Asp					Ile					CCA Pro		6517

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	CCA Pro	GAA Glu	TCA Ser 211	Met	GAC Asp	ACT Thr	CCA Pro	ACA Thr 211	Ser	ACA Thr	AGG Arg	AGG Arg	CGG Arg 212	Pro	AAA Lys	ACA Thr	6565
5			Gly					Val				TCA Ser 213	Ala				6613
10		Thr					Thr					GGA Gly O					6661
15	GGC Gly	ATC Ile	AAC Asn	GTG Val	TTC Phe 216	Arg	GAA Glu	ACT Thr	GCA Ala	AAA Lys 216.	Gln	AAA Lys	CTG Leu	GAC Asp	CCA Pro 2170	Ala	6709
20	GCA Ala	AGT Ser	GTA Val	ACT Thr 217	Gly	AGC Ser	AAG Lys	AGG Arg	CAG Gln 2180	Pro	AGA Arg	ACT Thr	CCT Pro	AAG Lys 218	Gly	AAA Lys	6757
				Leu					Gly			GAG Glu		Phe			6805
25	CCA Pro	GTA Val 220	Cys	ACT Thr	GAC Asp	AAG Lys	CCC Pro 221	Thr	ACT Thr	CAC His	GAG Glu	AAA Lys 2215	Thr	ACC Thr	AAA Lys	ATA Ile	6853
30		Cys					Pro					ACC Thr					6901
35	AAG Lys	CCA Pro	CAG G1n	TCC Ser	AAG Lys 2240	Arg	AGT Ser	CTC Leu	AGG Arg	AAA Lys 2245	Ala	GAC Asp	GTA Val	GAG Glu	GAA Glu 2250	Glu	6949
4 0					Arg					Ser		GGG Gly			Met		6997
,	ACA Thr	CCC Pro	AAA Lys 2270	Pro	GCA Ala	GGA Gly	GGT Gly	GAT Asp 2275	Glu	AAA Lys	GAC Asp	ATG Met	AAA Lys 2280	Ala	TTT Phe	ATG Met	7045
45	GGA Gly	ACT Thr 2285	Pro	GTG Val	CAG Gln	AAA Lys	TTG Leu 2290	Asp	CTG Leu	CCA Pro	GGA Gly	AAT Asn 2295	Leu	CCT Pro	GGC Gly	AGC Ser	7093
50		Arg					Pro					CAG Gln					7141
55						Glu					Pro	GGC Gly				Pro	7189
60					Lys					Ala		AAA Lys			Gln		7237
				Asp					Thr			CGG Arg		Lys			7285

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	CTC Leu	AGG Arg 236	Lys	GCA Ala	GAC Asp	GTA Val	GAG Glu 237	GAA Glu O	GAA Glu	TTT Phe	TTA Leu	GCA Ala 237	Leu	AGG Arg	AAA Lys	CGA Arg	7333
5		Pro					Ala	ATG Met				Lys					7381
10	GAT Asp	GAG Glu	AAA Lys	AAT Asn	ATC Ile 2400	Asn	ACA Thr	TTT Phe	GTG Val	GAA Glu 240	Thr	CCA Pro	GTG Val	CAG Gln	AAA Lys 241	Leu	7429
15	GAC Asp	CTG Leu	CTA Leu	GGA Gly 241	Asn	TTA Leu	CCT Pro	GGC Gly	AGC Ser 2420	Lys	AGA Arg	CAG Gln	CCA Pro	CAG Gln 242	Thr	CCT Pro	7477
20				Ala				GAG G1u 2435	Asp					Lys			7525
20			Thr					GAG Glu )					Asp				7573
25		Glu					Ser	CCA Pro				Ser					7621
30						Arg		AAG Lys			Leu					Met	7669
35					Leu			AGC Ser		Leu					Gly		7717
4 0				Thr				CCA Pro 2515	Thr					Ser			7765
10	GCG Ala	TTT Phe 2525	Lys	GAG Glu	TCT Ser	CCA Pro	AAG Lys 2530	CAG Gln )	ATC Ile	CTG Leu	GAC Asp	CCA Pro 2535	Ala	GCA Ala	AGT Ser	GTA Val	7813
45		Gly					Leu	AGA Arg				Glu					7861
50						Asp		AAA Lys			Phe					His	7909
55					Met			GAC Asp		Asn					Cys		7957
60				Pro				GAC Asp 2595	Thr					Lys			8005
,	CCC Pro	AAG Lys 2605	Thr	CGT Arg	CCC Pro	AGG Arg	AAA Lys 2610	GAA Glu	GTA Val	AAA Lys	GAG Glu	GAG Glu 2615	Leu	TCA Ser	GCA Ala	GTT Val	8053

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	GAG Glu 262	Arg	CTC Leu	ACG Thr	CAA G1n	ACA Thr 262	Ser	GGG G1y	CAA G1n	AGC Ser	ACA Thr 263	His	ACA Thr	CAC His	AAA Lys	GAA Glu 2635	8101
5				GGT Gly		Glu					Leu					Lys	8149
10	AAG Lys	AAA Lys	CCA Pro	AAC Asn 265	Pro	GTA Val	GAA Glu	GAG Glu	GAA Glu 266	Pro	AGC Ser	AGG Arg	AGA Arg	AGG Arg 266	Pro	AGA Arg	8197
15	GCA Ala	CCT Pro	AAG Lys 267	GAA Glu O	AAG Lys	GCC Ala	CAA Gln	CCC Pro 267	Leu	GAA Glu	GAC Asp	CTG Leu	GCC Ala 268	Gly	TTC Phe	ACA Thr	8245
20			Ser	GAA Glu				His					Leu				8293
20		Ala		AAA Lys			Cys					Leu					8341
25				AGC Ser		Lys					Thr					Va1	8389
30				GAA Glu 2735	Glu					Lys					Ser		8437
35				GAT Asp					Pro					Lys			8485
40			Leu	AAG Lys				Lys					Pro				8533
40		Thr		AGC Ser			Arg					Arg					8581
45				GAC Asp		Ala					Pro					Thr	8629
50	GAA Glu	GAA Glu	TCA Ser	ATG Met 2815	Thr	GAT Asp	GAC Asp	AAA Lys	ACC Thr 2820	Thr	AAA Lys	ATA Ile	CCC Pro	TGC Cys 2825	Lys	TCA Ser	8677
55				CTA Leu )					Thr					Arg			8725
60			Ala	CAG Gln				Val					Leu				8773
00		Leu		CAA Gln			Gly					Thr					8821

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						Gly		AAA Lys			Lys					Arg	8869
5					Glu			ATT Ile		Ser					Arg		8917
10				Lys				CTG Leu 291:	Glu					Phe			8965
15			Gln					ACT Thr					Asn				9013
20	GAT Asp 2940	Ser	TTT Phe	ACA Thr	AGC Ser	GCT Ala 2945	Pro	AAG Lys	CAA Gln	ACA Thr	CCT Pro 295	Asp	AGT Ser	GGA Gly	AAA Lys	CCT Pro 2955	9061
20						Arg		CTT Leu			Pro					Val	9109
25	GGA Gly	GAC Asp	GTG Val	GTA Val 297	Ser	ACC Thr	AGA Arg	GAC Asp	CCT Pro 2980	Val	AAA Lys	TCA Ser	CAA Gln	AGC Ser 2985	Lys	AGC Ser	9157
30	AAC Asn	ACT Thr	TCC Ser 2990	Leu	CCC Pro	CCA Pro	CTG Leu	CCC Pro 2995	Phe	AAG Lys	AGG Arg	GGA Gly	GGT Gly 3000	Gly	AAA Lys	GAT Asp	9205
35			Val					AGG Arg					Pro				9253
4 0	GAA G1u 3020	Ile	GTG Val	GAG Glu	GAG Glu	CTG Leu 3025	Pro	GCC Ala	AGC Ser	AAG Lys	AAG Lys 3030	Gln	AGG Arg	GTT Val	GCT Ala	CCC Pro 3035	9301
10	AGG Arg	GCA Ala	AGA Arg	GGC Gly	AAA Lys 3040	Ser	TCC Ser	GAA Glu	CCC Pro	GTG Val 3045	Val	ATC Ile	ATG Met	AAG Lys	AGA Arg 3050	Ser	9349
45					Ala			ATT Ile		Pro					Asn		9397
50	AAC Asn	GAC Asp	ATG Met 3070	Lys	ACC Thr	AAC Asn	AAA Lys	GAG Glu 3075	Glu	CAC His	AAA Lys	TTA Leu	CAA Gln 3080	Asp	TCG Ser	GTC Val	9445
55	CCT Pro	GAA Glu 3085	Asn	AAG Lys	GGA Gly	ATA Ile	TCC Ser 3090	CTG Leu	CGC Arg	TCC Ser	AGA Arg	CGC Arg 3095	Gln	GAT Asp	AAG Lys	ACT Thr	9493
5 0		Ala					Thr	GAG Glu				Leu					9541
JU	GAA Glu	ATA Ile	AAC Asn	AGA Arg	AAT Asn 3120	Glu	AAG Lys	AAG Lys	Pro	ATG Met 3125	Lys	ACC Thr	TCC Ser	CCA Pro	GAG Glu 3130	Met	9589

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	GAC ATT CAG AAT CCA GAT GAT GGA GCC CGG AAA CCC ATA CC Asp Ile Gln Asn Pro Asp Asp Gly Ala Arg Lys Pro Ile Pro 3135 3140 31		9637
5	AAA GTC ACT GAG AAC AAA AGG TGC TTG AGG TCT GCT AGA CA Lys Val Thr Glu Asn Lys Arg Cys Leu Arg Ser Ala Arg G 3150 3155 3160	AG AAT GAG ln Asn Glu	9685
10	AGC TCC CAG CCT AAG GTG GCA GAG GAG AGC GGA GGG CAG AA Ser Ser Gln Pro Lys Val Ala Glu Glu Ser Gly Gly Gln Ly 3165 3170 3175	AG AGT GCG /s Ser Ala	9733
15	AAG GTT CTC ATG CAG AAT CAG AAA GGG AAA GGA GAA GCA GC Lys Val Leu Met Gln Asn Gln Lys Gly Lys Gly Glu Ala Gl 3180 3185 3190	GA AAT TCA Ly Asn Ser 3195	9781
20	GAC TCC ATG TGC CTG AGA TCA AGA AAG ACA AAA AGC CAG CC Asp Ser Met Cys Leu Arg Ser Arg Lys Thr Lys Ser Gln Pr 3200 3205		9829
20	AGC ACT TTG GAG AGC AAA TCT GTG CAG AGA GTA ACG CGG AC Ser Thr Leu Glu Ser Lys Ser Val Gln Arg Val Thr Arg Se		9877
25	AGG TGT GCA GAA AAT CCA AAG AAG GCT GAG GAC AAT GTG TG Arg Cys Ala Glu Asn Pro Lys Lys Ala Glu Asp Asn Val Cy 3230 3235 3240	GT GTC AAG rs Val Lys	9925
30	AAA ATA ACA ACC AGA AGT CAT AGG GAC AGT GAA GAT ATT TO Lys Ile Thr Thr Arg Ser His Arg Asp Ser Glu Asp Ile 3245 3250 3255	ACAGAAAA	9974
	ATCGAACTGG GAAAAATATA ATAAAGTTAG TTTTGTGATA AGTTCTAGTG	CAGTTTTTGT	10034
35	CATAAATTAC AAGTGAATTC TGTAAGTAAG GCTGTCAGTC TGCTTAAGGG	AAGAAAACTT	10094
	TGGATTTGCT GGGTCTGAAT CGGCTTCATA AACTCCACTG GGAGCACTGC	TGGGCTCCTG	10154
40	GACTGAGAAT AGTTGAACAC CGGGGGCTTT GTGAAGGAGT CTGGGCCAAG	GTTTGCCCTC	10214
40	AGCTTTGCAG AATGAAGCCT TGAGGTCTGT CACCACCCAC AGCCACCCTA	CAGCAGCCTT	10274
	AACTGTGACA CTTGCCACAC TGTGTCGTCG TTTGTTTGCC TATGTTCTCC	AGGGCACGGT	10334
45	GGCAGGAACA ACTATCCTCG TCTGTCCCAA CACTGAGCAG GCACTCGGTA	AACACGAATG	10394
	AATGGATAAG CGCACGGATG AATGGAGCTT ACAAGATCTG TCTTTCCAAT	GGCCGGGGGC	10454
50	ATTTGGTCCC CAAATTAAGG CTATTGGACA TCTGCACAGG ACAGTCCTAT	TTTTGATGTC	10514
50	CTTTCCTTTC TGAAAATAAA GTTTTGTGCT TTGGAGAATG ACTCGTGAGC	ACATCTTTAG	10574
	GGACCAAGAG TGACTTTCTG TAAGGAGTGA CTCGTGGCTT GCCTTGGTCT	CTTGGGAATA	10634
55	CTTTTCTAAC TAGGGTTGCT CTCACCTGAG ACATTCTCCA CCCGCGGAAT	CTCAGGGTCC	10694
	CAGGCTGTGG GCCATCACGA CCTCAAACTG GCTCCTAATC TCCAGCTTTC	CTGTCATTGA	10754
60	AAGCTTCGGA AGTTTACTGG CTCTGCTCCC GCCTGTTTTC TTTCTGACTC	TATCTGGCAG	10814
00	CCCGATGCCA CCCAGTACAG GAAGTGACAC CAGTACTCTG TAAAGCATCA	TCATCCTTGG	10874
	AGAGACTGAG CACTCAGCAC CTTCAGCCAC GATTTCAGGA TCGCTTCCTT	GTGAGCCGCT	10934

	GCCTCCGAAA	TCTCCTTTGA	AGCCCAGACA	TCTTTCTCCA	GCTTCAGACT	TGTAGATATA	10994
	ACTCGTTCAT	CTTCATTTAC	TTTCCACTTT	GCCCCCTGTC	CTCTCTGTGT	TCCCCAAATC	11054
5	AGAGAATAGC	CCGCCATCCC	CCAGATCACC	TGTCTGGATT	CCTCCCCATT	CACCCACCTT	11114
	GCCAGGTGCA	GGTGAGGATG	GTGCACCAGA	CAGGGTAGCT	GTCCCCCAAA	ATGTGCCCTG	11174
10	TGCGGGCAGT	GCCCTGTCTC	CACGTTTGTT	TCCCCAGTGT	CTGGCGGGGA	GCCAGGTGAC	11234
10	ATCATAAATA	CTTGCTGAAT	GAATGCAGAA	ATCAGCGGTA	CTGACTTGTA	CTATATTGGC	11294
	TGCCATGATA	GGGTTCTCAC	AGCGTCATCC	ATGATCGTAA	GGGAGAATGA	CATTCTGCTT	11354
15	GAGGGAGGGA	ATAGAAAGGG	GCAGGGAGGG	GACATCTGAG	GGCTTCACAG	GGCTGCAAAG	11414
	GGTACAGGGA	TTGCACCAGG	GCAGAACAGG	GGAGGGTGTT	CAAGGAAGAG	TGGCTCTTAG	11474
20	CAGAGGCACT	TTGGAAGGTG	TGAGGCATAA	ATGCTTCCTT	CTACGTAGGC	CAACCTCAAA	11534
20	ACTTTCAGTA	GGAATGTTGC	TATGATCAAG	TTGTTCTAAC	ACTTTAGACT	TAGTAGTAAT	11594
	TATGAACCTC	ACATAGAAAA	ATTTCATCCA	GCCATATGCC	TGTGGAGTGG	AATATTCTGT	11654
25	TTAGTAGAAA	AATCCTTTAG	AGTTCAGCTC	TAACCAGAAA	TCTTGCTGAA	GTATGTCAGC	11714
	ACCTTTTCTC	ACCCTGGTAA	GTACAGTATT	TCAAGAGCAC	GCTAAGGGTG	GTTTTCATTT	11774
30	TACAGGGCTG	TTGATGATGG	GTTAAAAATG	TTCATTTAAG	GGCTACCCCC	GTGTTTAATA	11834
30	GATGAACACC	ACTTCTACAC	AACCCTCCTT	GGTACTGGGG	GAGGGAGAGA	TCTGACAAAT	11894
	ACTGCCCATT	CCCCTAGGCT	GACTGGATTT	GAGAACAAAT	ACCCACCCAT	TTCCACCATG	11954
35	GTATGGTAAC	TTCTCTGAGC	TTCAGTTTCC	AAGTGAATTT	CCATGTAATA	GGACATTCCC	12014
	ATTAAATACA	AGCTGTTTTT	ACTTTTTCGC	CTCCCAGGGC	CTGTGCGATC	TGGTCCCCCA	12074
40	GCCTCTCTTG	GGCTTTCTTA	CACTAACTCT	GTACCTACCA	TCTCCTGCCT	CCCTTAGGCA	12134
	GGCACCTCCA	ACCACCACAC	ACTCCCTGCT	GTTTTCCCTG	CCTGGAACTT	TCCCACCAGC	12194
	CCCACCAAGA	TCATTTCATC	CAGTCCTGAG	CTCAGCTTAA	GGGAGGCTTC	TTGCCTGTGG	12254
45	GTTCCCTCAC	CCCCATGCCT	GTCCTCCAGG	CTGGGGCAGG	TTCTTAGTTT	GCCTGGAATT	12314
	GTTCTGTACC	TCTTTGTAGC	ACGTAGTGTT	GTGAAACTAA	GCCACTAATT	GAGTTTCTGG	12374
50	CTCCCCTCCT	GGGGTTGTAA	GTTTTGTTCA	TTCATGAGGG	CCGACTGTAT	TTCCTGGTTA	12434
~ ~	CTGTATCCCA	GTGACCAGCC	ACAGGAGATG	TCCAATAAAG	TATGTGATGA	AATGGTCTT	12493

(2) INFORMATION FOR SEQ ID NO: 2:

55

60

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3256 amino acids
  (B) TYPE: amino acid
  (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: Protein
  (xi) SEQUENCE DISCRIPTION: SEQ ID NO: 2:
- Met Trp Pro Thr Arg Arg Leu Val Thr Ile Lys Arg Ser Gly Val Asp 65

Gly Pro His Phe Pro Leu Ser Leu Ser Thr Cys Leu Phe Gly Arg Gly Ile Glu Cys Asp Ile Arg Ile Gln Leu Pro Val Val Ser Lys Gln His 5 Cys Lys Val Glu Ile His Glu Gln Glu Ala Ile Leu His Asn Phe Ser Ser Thr Asn Pro Thr Gln Val Asn Gly Ser Val Ile Asp Glu Pro Val 65 70 75 80 10 Arg Leu Lys His Gly Asp Val Ile Thr Ile Ile Asp Arg Ser Phe Arg 15 Tyr Glu Asn Glu Ser Leu Gln Asn Gly Arg Lys Ser Thr Glu Phe Pro 100 105 110Arg Lys Ile Arg Glu Gln Glu Pro Ala Arg Arg Val Ser Arg Ser Ser 20 Phe Ser Ser Asp Pro Asp Glu Lys Ala Gln Asp Ser Lys Ala Tyr Ser 130 135 140 Lys Ile Thr Glu Gly Lys Val Ser Gly Asn Pro Gln Val His Ile Lys 145 150 155 Asn Val Lys Glu Asp Ser Thr Ala Asp Asp Ser Lys Asp Ser Val Ala 165 170 175 30 Gln Gly Thr Thr Asn Val His Ser Ser Glu His Ala Gly Arg Asn Gly 180 185 190Arg Asn Ala Ala Asp Pro Ile Ser Gly Asp Phe Lys Glu Ile Ser Ser 35 200 Val Lys Leu Val Ser Arg Tyr Gly Glu Leu Lys Ser Val Pro Thr Thr 210 220 40 Gln Cys Leu Asp Asn Ser Lys Lys Asn Glu Ser Pro Phe Trp Lys Leu Tyr Glu Ser Val Lys Lys Glu Leu Asp Val Lys Ser Gln Lys Glu Asn 45 Val Leu Gln Tyr Cys Arg Lys Ser Gly Leu Gln Thr Asp Tyr Ala Thr 260 265 270 Glu Lys Glu Ser Ala Asp Gly Leu Gln Gly Glu Thr Gln Leu Leu Val 50 280 Ser Arg Lys Ser Arg Pro Lys Ser Gly Gly Ser Gly His Ala Val Ala 290 295 300 55 Glu Pro Ala Ser Pro Glu Gln Glu Leu Asp Gln Asn Lys Gly Lys Gly 310 Arg Asp Val Glu Ser Val Gln Thr Pro Ser Lys Ala Val Gly Ala Ser 60 Phe Pro Leu Tyr Glu Pro Ala Lys Met Lys Thr Pro Val Gln Tyr Ser 345

Gln Gln Asn Ser Pro Gln Lys His Lys Asn Lys Asp Leu Tyr Thr 360 Thr Gly Arg Arg Glu Ser Val Asn Leu Gly Lys Ser Glu Gly Phe Lys 5 Ala Gly Asp Lys Thr Leu Thr Pro Arg Lys Leu Ser Thr Arg Asn Arg 10 Thr Pro Ala Lys Val Glu Asp Ala Ala Asp Ser Ala Thr Lys Pro Glu 410 Asn Leu Ser Ser Lys Thr Arg Gly Ser Ile Pro Thr Asp Val Glu Val 15 Leu Pro Thr Glu Thr Glu Ile His Asn Glu Pro Phe Leu Thr Leu Trp Leu Thr Gln Val Glu Arg Lys Ile Gln Lys Asp Ser Leu Ser Lys Pro 20 Glu Lys Leu Gly Thr Thr Ala Gly Gln Met Cys Ser Gly Leu Pro Gly 465 470 475 470 Leu Ser Ser Val Asp Ile Asn Asn Phe Gly Asp Ser Ile Asn Glu Ser Glu Gly Ile Pro Leu Lys Arg Arg Val Ser Phe Gly Gly His Leu 500 505 510 30 Arg Pro Glu Leu Phe Asp Glu Asn Leu Pro Pro Asn Thr Pro Leu Lys Arg Gly Glu Ala Pro Thr Lys Arg Lys Ser Leu Val Met His Thr Pro 35 535 Pro Val Leu Lys Lys Ile Ile Lys Glu Gln Pro Gln Pro Ser Gly Lys Gln Glu Ser Gly Ser Glu Ile His Val Glu Val Lys Ala Gln Ser Leu Val Ile Ser Pro Pro Ala Pro Ser Pro Arg Lys Thr Pro Val Ala Ser 45 Asp Gln Arg Arg Arg Ser Cys Lys Thr Ala Pro Ala Ser Ser Lys 600 Ser Gln Thr Glu Val Pro Lys Arg Gly Glu Arg Val Ala Thr Cys 50 615 Leu Gln Lys Arg Val Ser Ile Ser Arg Ser Gln His Asp Ile Leu Gln Met Ile Cys Ser Lys Arg Arg Ser Gly Ala Ser Glu Ala Asn Leu Ile Val Ala Lys Ser Trp Ala Asp Val Val Lys Leu Gly Ala Lys Gln Thr 60 Gln Thr Lys Val Ile Lys His Gly Pro Gln Arg Ser Met Asn Lys Arg 680 Gln Arg Arg Pro Ala Thr Pro Lys Lys Pro Val Gly Glu Val His Ser 65

	G1n 705		Ser	Thr	G1y	His 710		Asn	Ser	Pro	Cys 715		Ile	Ile	Ile	G1 72
5	Lys	Ala	His	Thr	Glu 725	Lys	Va1	His	Val	Pro 730		Arg	, Pro	Tyr	Arg 735	
	Leu	Asn	Asn	Phe 740	Ile	Ser	Asn	Gln	Lys 745		Asp	Phe	Lys	G1u 750		Le
10	Ser	Gly	Ile 755	Ala	Glu	Met	Phe	Lys 760		Pro	Val	Lys	G1u 765		Pro	G1ı
15 <sup>°</sup>	Leu	Thr 770	Ser	Thr	Cys	His	Ile 775		Ile	Ser	Asn	Ser 780		Asn	Leu	Le
13	Gly 785	Lys	Gln	Phe	Gln	G1y 790	Thr	Asp	Ser	Gly	Glu 795	Glu	Pro	Leu	Leu	Pro 800
20	Thr	Ser	Glu	Ser	Phe 805	Gly	Gly	Asn	Val	Phe 810	Phe	Ser	Ala	Gln	Asn 815	
	A1a	Lys	G1n	Pro 820	Ser	Asp	Lys	Cys	Ser 825	Ala	Ser	Pro	Pro	Leu 830	Arg	Arg
25	G1n	Cys	Ile 835	Arg	Glu	Asn	G1y	Asn 840	Val	Ala	Lys	Thr	Pro 845	Arg	Asn	Thr
30	Tyr	Lys 850	Met	Thr	Ser	Leu	G1u 855	Thr	Lys	Thr	Ser	Asp 860	Thr	G1u	Thr	G1u
50	Pro 865	Ser	Lys	Thr	Val	Ser 870	Thr	Val	Asn	Arg	Ser 875	Gly	Arg	Ser	Thr	Glu 880
35	Phe	Arg	Asn	Ile	Gln 885	Lys	Leu	Pro	Val	Glu 890	Ser	Lys	Ser	G1u	G1u 895	Thr
٠	Asn	Thr	Glu	Ile 900	Va1	Glu	Cys	Ile	Leu 905	Lys	Arg	G1y	G1n	Lys 910	Ala	Thr
40	Leu	Leu	Gln 915	Gln	Arg	Arg	Glu	Gly 920	Glu	Met	Lys	G1u	Ile 925	Glu	Arg	Pro
4.5	Phe	Glu 930	Thr	Tyr	Lys	Glu	Asn 935	Ile	G1u	Leu	Lys	Glu 940	Asn	Asp	Glu	Lys
	Met 945	Lys	Ala	Met	Lys	Arg 950	Ser	Arg	Thr	Trp	Gly 955	Gln	Lys	Cys	Ala	Pro 960
50	Met	Ser	Asp	Leu	Thr 965	Asp	Leu	Lys	Ser	Leu 970	Pro	Asp	Thr	Glu	Leu 975	Met
	Lys	Asp	Thr	Ala 980	Arg	Gly	Gln	Asn	Leu 985	Leu	G1n	Thr	G1n	Asp 990	His	Ala
55	Lys	Ala	Pro 995	Lys	Ser	Glu	Lys	Gly 1000		Ile	Thr	Lys	Met 1005		Cys	G1n
50	Ser	Leu 1010	Gln )	Pro	Glu	Pro	Ile 1015	Asn	Thr	Pro	Thr	His 1020		Lys	G1n	Gln
<del>-</del>	Leu 1025	Lys	Ala	Ser	Leu	Gly 1030		Val	G1y	Va1	Lys 1035		Glu	Leu	Leu	Ala 104

	Val	G1y	Lys	Phe	Thr 104		Thr	Ser	Gly	Glu 105		Thr	His	Thr	His 105	_
5	Glu	Pro	Ala	Gly 1060		Gly	Lys	Ser	Ile 106		Thr	Phe	Lys	Glu 107		Pro
	Lys	G1n	Ile 107		Asp	Pro	Ala	Ala 108		Val	Thr	Gly	Met 108		Lys	Trp
10	Pro	Arg 109		Pro	Lys	G1u	Glu 109	Ala 5	Gln	Ser	Leu	Glu 1100		Leu	Ala	Gly
	Phe 1105		Glu	Leu	Phe	Gln 1110		Pro	Gly	Pro	Ser 111:		Glu	Ser	Met	Thr 1120
15	Asp	Glu	Lys	Thr	Thr 1125		Ile	Ala	Cys	Lys 1130		Pro	Pro	Pro	Glu 113	
20	Val	Asp	Thr	Pro 1140		Ser	Thr	Lys	Gln 1145		Pro	Lys	Arg	Ser 1150		Arg
	Lys	Ala	Asp 1155		Glu	G1u	G1u	Phe 1160		Ala	Leu	Arg	Lys 1165		Thr	Pro
25	Ser	Ala 1170		Lys	Ala	Met	Leu 1175	Thr	Pro	Lys	Pro	Ala 1180		G1y	Asp	Glu
30	Lys 1185		Ile	Lys	Ala	Phe 1190		G1y	Thr	Pro	Val 1195		Lys	Leu	Asp	Leu 1200
30	Ala	Gly	Thr	Leu	Pro 1205		Ser	Lys	Arg	Gln 1210		Gln	Thr	Pro	Lys 121	
35	Lys	Ala	Gln	Ala 1220		Glu	Asp	Leu	Ala 1225		Phe	Lys	Glu	Leu 1230		Gln
	Thr	Pro	Gly 1235		Thr	G1u	G1u	Leu 1240		Ala	Ala	Gly	Lys 1245		Thr	Lys
40	Ile	Pro 1250		Asp	Ser	Pro	Gln 1255	Ser	Asp	Pro	Val	Asp 1260		Pro	Thr	Ser
45	Thr 1265		Gln	Arg	Pro	Lys 1270		Ser	Ile	Arg	Lys 1275		Asp	Val	Glu	Gly 1280
4.0	Glu	Leu	Leu	Ala	Cys 1285		Asn	Leu	Met	Pro 1290		Ala	Gly	Lys	Ala 1295	
50	His	Thr	Pro	Lys 1300		Ser	Val	Gly	Glu 1305		Lys	Asp	Ile	Ile 1310		Phe
	Va1	Gly	Thr 1315		Val	Gln	Lys	Leu 1320	Asp	Leu	Thr	Glu	Asn 1325		Thr	G1y
55	Ser	Lys 1330		Arg	Pro	Gln	Thr 1335		Lys	Glu	G1u	Ala 1340		Ala	Leu	Glu `
60	Asp 1345		Thr	Gly	Phe	Lys 1350		Leu	Phe	Gln	Thr 1355		Gly	His	Thr	Glu 1360
00	G1u	Ala	Val	Ala	Ala 1365		Lys	Thr	Thr	Lys 1370		Pro	Cys	G1u	Ser 1375	
65	Pro	Pro	Glu	Ser 1380		Asp	Thr	Pro	Thr 1385		Thr	Arg	Arg	Gln 1390		Lys

		Thr	Pro	Leu 1395		Lys	Arg	Asp	Val 140		Lys	Glu	Leu	Ser 140		Leu	Lys
	5	Lys	Leu 1410	Thr	Gln	Thr	Ser	Gly 141		Thr	Thr	His	Thr 142		Lys	Va1	Pro
		Gly 1425		Glu	Asp	Lys	Ser 1430		Asn	Ala	Phe	Arg 1435	Glu 5	Thr	Ala	Lys	Gln 144
	10.	Lys	Leu	Asp	Pro	Ala 1445		Ser	Val	Thr	Gly 1450		Lys	Arg	His	Pro 145	
	16	Thr	Lys	Glu	Lys 1460		Gln	Pro	Leu	Glu 146	Asp 5	Leu	Ala	Gly	Trp 147		Glu
	15	Leu	Phe	Gln 1475		Pro	Val	Cys	Thr 1480		Lys	Pro	Thr	Thr 148		Glu	Lys
	20	Thr	Thr 1490	Lys	Ile	A1a	Cys	Arg 1495		G1n	Pro	Asp	Pro 1500		Asp	Thr	Pro
		Thr 1505		Ser	Lys	Pro	Gln 1510		Lys	Arg	Ser	Leu 1515		Lys	Val	Asp	Val 152
	25	G1u	G1u	Glu	Phe	Phe 1525		Leu	Arg	Lys	Arg 1530		Pro	Ser	Ala	Gly 1535	
	30	Ala	Met	His	Thr 1540		Lys	Pro	Ala	Val 1545		Gly	Glu	Lys	Asn 1550		Tyr
		Ala	Phe	Met 1555		Thr	Pro	Val	Gln 1560		Leu	Asp	Leu	Thr 1565		Asn	Leu
	35	Thr	Gly 1570	Ser )	Lys	Arg	Arg	Leu 1575		Thr	Pro	Lys	Glu 1580		Ala	Gln	Ala
		Leu 1585		Asp	Leu	Ala	Gly 1590		Lys	Glu	Leu	Phe 1595		Thr	Arg	Gly	His 1600
	40	Thr	G1u	Glu	Ser	Met 1605		Asn	Asp	Lys	Thr 1610		Lys	Val	Ala	Cys 1615	
,	45	Ser	Ser	Gln	Pro 1620		Leu	Asp	Lys	Asn 1625		Ala	Ser	Ser	Lys 1630		Arg
		Leu	Lys	Thr 1635		Leu	G1y	Lys	Val 1640		Val	Lys	Glu	Glu 1645		Leu	Ala
	50	Val	Gly 1650	Lys )	Leu	Thr	Gln	Thr 1655		Gly	Glu	Thr	Thr 1660		Thr	His	Thr
		Glu 1665		Thr	G1y	Asp	Gly 1670		Ser	Met	Lys	Ala 1675		Met	Glu	Ser	Pro 1680
	55	Lys	Gln	Ile	Leu	Asp 1685		Ala	Ala	Ser	Leu 1690		Gly	Ser	Lys	Arg 1695	
	60	Leu	Arg	Thr	Pro 1700		G1y	Lys	Ser	Glu 1705		Pro	Glu	Asp	Leu 1710		Gly
		Phe	Ile	Glu 1715		Phe	Gln		Pro		His	Thr	Lys	Glu		Met	Thr

	Asn	Glu 173		Thr	Thr	Lys	Val 173		Tyr	Arg	Ala	Ser 174		Pro	Asp	Leu
5	Val 174		Thr	Pro	Thr	Ser 1750		Lys	Pro	Gln	Pro 175		Arg	Ser	Leu	Arg 1760
	Lys	Ala	Asp	Thr	Glu 176		Glu	Phe	Leu	Ala 177		Arg	Lys	Gln	Thr 177	
10	Ser	Ala	G1y	Lys 1780		Met	His	Thr	Pro 1785		Pro	Ala	Val	Gly 1790		G1u
1.5	Lys	Asp	Ile 179		Thr	Phe	Leu	Gly 1800		Pro	Val	G1n	Lys 180		Asp	Gln
15	Pro	Gly 1810		Leu	Pro	G1y	Ser 1815		Arg	Arg	Leu	Gln 1820		Arg	Lys	Glu
20	Lys 1825		G1n	Ala	Leu	Glu 1830		Leu	Thr	G1y	Phe 1835		Glu	Leu	Phe	Gln 1840
	Thr	Pro	Cys	Thr	Asp 1845		Pro	Thr	Ala	Asp 1850		Lys	Thr	Thr	Lys 185	
25	Ile	Leu	Cys	Lys 1860		Pro	Gln	Ser	Asp 1865		Ala	Asp	Thr	Pro 1870		Asn
30	Thr	Lys	Gln 1875	Arg 5	Pro	Lys	Arg	Ser 1880		Lys	Lys	Ala	Asp 1885		Glu	Glu
30	Glu	Phe 1890		Ala	Phe	Arg	Lys 1895		Thr	Pro	Ser	Ala 1900	-	Lys	Ala	Met
35	His 1905		Pro	Lys	A1a	Ala 1910		Gly	Glu	Glu	Lys 1915		Ile	Asn	Thr	Phe 1920
	Val	Gly	Thr	Pro	Val 1925		Lys	Leu	Asp	Leu 1930		G1y	Asn	Leu	Pro 1935	
40	Ser	Lys	Arg	Arg 1940		Gln	Thr	Pro	Lys 1945		Lys	Ala	Lys	Ala 1950		Glu
45	Asp	Leu	Ala 1955	Gly 5	Phe	Lys	Glu	Leu 1960		Gln	Thr	Pro	Gly 1965		Thr	Glu
43	G1u	Ser 1970		Thr	Asp	Asp	Lys 1975		Thr	G1u	Val	Ser 1980		Lys	Ser	Pro
50	Gln 1985	Pro	Asp	Pro	Val	Lys 1990	Thr	Pro	Thr	Ser	Ser 1995	Lys	Gln	Arg	Leu	Lys 2000
	Ile	Ser	Leu	Gly	Lys 2005		Gly	Val	Lys	Glu 2010		Val	Leu	Pro	Val 2015	
55	Lys	Leu	Thr	Gln 2020		Ser	Gly	Lys	Thr 2025		G1n	Thr	His	Arg 2030		Thr
60	Ala	Gly	Asp 2035	Gly 5	Lys	Ser	Ile	Lys 2040		Phe	Lys	Glu	Ser 2045		Lys	Gln
0.0	Met	Leu 2050		Pro	Ala	Asn	Tyr 2055		Thr	Gly	Met	Glu 2060		Trp	Pro	Arg
65	Thr 2065		Lys	Glu	Glu	Ala 2070		Ser	Leu	Glu	Asp 2075		Ala	Gly	Phe	Lys 2080

	Glu	Leu	Phe	Gln	Thr 208		Asp	His	Thr	Glu 209	Glu O	Ser	Thr	Thr	Asp 209	
5	Lys	Thr	Thr	Lys 210		Ala	Cys	Lys	Ser 210		Pro	Pro	Glu	Ser 211		Asp
	Thr	Pro	Thr 211		Thr	Arg	Arg	Arg 212		Lys	Thr	Pro	Leu 212		Lys	Arg
10	Asp	Ile 213	Val 0	Glu	G1u	Leu	Ser 213		Leu	Lys	G1n	Leu 214		Gln	Thr	Thr
15	His 214	Thr 5	Asp	Lys	Val	Pro 215		Asp	Glu	Asp	Lys 215		Ile	Asn	Va1	Phe 2160
13	Arg	G1u	Thr	Ala	Lys 216	G1n 5	Lys	Leu	Asp	Pro 217	Ala O	Ala	Ser	Val	Thr 217	
20	Ser	Lys	Arg	G1n 218		Arg	Thr	Pro	Lys 218		Lys	Ala	G1n	Pro 219		Glu
	Asp	Leu	Ala 219	Gly 5	Leu	Lys	Glu	Leu 220		Gln	Thr	Pro	Val 220		Thr	Asp
25	Lys	Pro 221		Thr	His	Glu	Lys 221		Thr	Lys	Ile	A1a 2220		Arg	Ser	Pro
30	Gln 222	Pro 5	Asp	Pro	Val	Gly 2230		Pro	Thr	Ile	Phe 2235		Pro	Gln	Ser	Lys 2240
2	Arg	Ser	Leu	Arg	Lys 2245		Asp	Va1	Glu	Glu 2250	Glu O	Ser	Leu	Ala	Leu 2255	
35	Lys	Arg	Thr	Pro 2260		Val	Gly	Lys	A1a 226		Asp	Thr	Pro	Lys 227		Ala
	Gly	Gly	Asp 2275	Glu 5	Lys	Asp	Met	Lys 2280		Phe	Met	G1y	Thr 2285		Val	Gln
40	Lys	Leu 2290	Asp O	Leu	Pro	Gly	Asn 2295		Pro	G1y	Ser	Lys 2300		Trp	Pro	Gln
45	Thr 2305	Pro	Lys	Glu	Lys	Ala 2310		Ala	Leu	Glu	Asp 2315		Ala	Gly	Phe	Lys 2320
13	Glu	Leu	Phe	Gln	Thr 2325	Pro	Gly	Thr	Asp	Lys 2330	Pro )	Thr	Thr	Asp	Glu 2335	
50	Thr	Thr	Lys	Ile 2340	Ala )	Cys	Lys	Ser	Pro 2345		Pro	Asp	Pro	Val 2350		Thr
	Pro	Ala	Ser 2355	Thr	Lys	Gln	Arg	Pro 2360	Lys )	Arg	Asn	Leu	Arg 2365		Ala	Asp
55	Val	Glu 2370	Glu )	Glu	Phe	Leu	Ala 2375	Leu	Arg	Lys	Arg	Thr 2380		Ser	Ala	Gly
60	Lys 2385	Ala	Met	Asp	Thr	Pro 2390	Lys	Pro	Ala	Val	Ser 2395		G1u	Lys	Asn	Ile 2400
	Asn	Thr	Phe	Val	G1u 2405		Pro	Val	Gln	Lys 2410	Leu	Asp	Leu	Leu	Gly 2415	

	Leu	Pro	Gly	Ser 242		Arg	G1n	Pro	G1n 242		Pro	Lys	Glu	Lys 243		Glu
5	Ala	Leu	Glu 243	Asp 5	Leu	Va1	G1y	Phe		Glu	Leu	Phe	Gln 244		Pro	Gly
	His	Thr 245		Glu	Ser	Met	Thr 245	Asp 5	Asp	Lys	Ile	Thr 246		Val	Ser	Cys
10	Lys 246	Ser 5	Pro	Gln	Pro	G1u 247		Phe	Lys	Thr	Ser 247		Ser	Ser	Lys	Gln 2480
1.5	Arg	Leu	Lys	Ile	Pro 248	Leu 5	Val	Lys	Val	Asp 249		Lys	Glu	Glu	Pro 249	
15	Ala	Va1	Ser	Lys 250		Thr	Arg	Thr	Ser 2505		Glu	Thr	Thr	Gln 251		His
20	Thr	G1u	Pro 251	Thr 5	Gly	Asp	Ser	Lys 2520	Ser	Ile	Lys	Ala	Phe 252		G1u	Ser
	Pro	Lys 253	Gln 0	Ile	Leu	Asp	Pro 253	Ala 5	Ala	Ser	Val	Thr 254		Ser	Arg	Arg
25	G1n 2545	Leu 5	Arg	Thr	Arg	Lys 2550		Lys	Ala	Arg	Ala 255		Glu	Asp	Leu	Val 2560
30	Asp	Phe	Lys	Glu	Leu 2565		Ser	Ala	Pro	Gly 2570		Thr	Glu	Glu	Ser 257	
30	Thr	Ile	Asp	Lys 2580		Thr	Lys	Ile	Pro 2585		Lys	Ser	Pro	Pro 2590		Glu
35	Leu	Thr	Asp 259	Thr 5	Ala	Thr	Ser	Thr 2600	Lys )	Arg	Cys	Pro	Lys 2605		Arg	Pro
	Arg	Lys 261		Va1	Lys	Glu	Glu 261	Leu 5	Ser	Ala	Va1	G1u 2620		Leu	Thr	Gln
40	Thr 2625	Ser	Gly	Gln	Ser	Thr 2630		Thr	His	Lys	Glu 2635		Ala	Ser	Gly	Asp 2640
45	Glu	Gly	Ile	Lys	Val 2645	Leu	Lys	Gln	Arg	Ala 2650		Lys	Lys	Pro	Asn 2655	
43	Val	G1u	Glu	G1u 2660	Pro	Ser	Arg	Arg	Arg 2665		Arg	Ala	Pro	Lys 2670		Lys
50	Ala	Gln	Pro 2675		Glu	Asp	Leu	Ala 2680		Phe	Thr	G1u	Leu 2685		Glu	Thr
	Ser	Gly 2690	His	Thr	Gln	Glu	Ser 2695	Leu	Thr	Ala	Gly	Lys 2700		Thr	Lys	Ile
55	Pro 2705	Cys	Glu	Ser	Pro	Pro 2710		Glu	Va1	Val	Asp 2715		Thr	Ala	Ser	Thr 2720
60	Lys	Arg	His	Leu	Arg 2725	Thr	Arg	Va1	Gln	Lys 2730		Gln	Va1	Lys	Glu 2735	
23	Pro	Ser	Ala	Val 2740	Lys	Phe	Thr	Gln	Thr 2745	Ser	Gly	Glu	Thr	Thr 2750		Ala
65	Asp	Lys	G1u 2755	Pro	Ala	Gly	Glu	Asp 2760		Gly	Ile		Ala 2765		Lys	Glu

	Ser	Ala 277	Lys 0	G1n	Thr	Pro	A1a 277	Pro 5	Ala	Ala	Ser	Va1 278		Gly	Ser	Arg
5	Arg 278	Arg 5	, Pro	`Arg	Ala	Pro 279	Arg 0	Glu	Ser	Ala	G1n 279		Ile	Glu	Asp	Leu 2800
	Ala	G1y	Phe	Lys	Asp 280	Pro 5	Ala	Ala	Gly	His 281	Thr 0	Glu	Glu	Ser	Met 281	Thr 5
10	Asp	Asp	Lys	Thr 282	Thr 0	Lys	Ile	Pro	Cys 282	Lys 5	Ser	Ser	Pro	G1u 283		Glu
15	Asp	Thr	Ala 283	Thr 5	Ser	Ser	Lys	Arg 284		Pro	Arg	Thr	Arg 284		Gln	Lys
13	Val	Glu 285	Val 0	Lys	Glu	Glu	Leu 285	Leu 5	Ala	Val	Gly	Lys 286		Thr	Gln	Thr
20	Ser 286	G1y 5	Glu	Thr	Thr	His 287	Thr 0	Asp	Lys	Glu	Pro 287		Gly	Glu	G1y	Lys 2880
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	Arg	Va1	Leu	Arg	Ala 2965	Pro	Lys	Val	Glu	Pro 2970		G1y	Asp	Val	Val 2975	
40	Thr	Arg	Asp	Pro 2980		Lys	Ser	G1n	Ser 2985		Ser	Asn	Thr	Ser 2990		Pro
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43	Thr	Lys 3010	Arg	Leu	Arg	Cys	Met 3015		Ala	Pro	Glu	Glu 3020		Val	Glu	G1u
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55	Lys	Arg	Ile	G1u 3060	Pro	Ala	Glu	Glu	Leu 3065		Ser	Asn	Asp	Met 3070		Thr
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	Ile 310	Thr 5	Glu	Val	Phe	Val 3110		Ala	Glu	Arg	Ile 311:		Ile	Asn	Arg	Asn 3120
5	Glu	Lys	Lys	Pro	Met 3125	Lys	Thr	Ser	Pro	Glu 3130		Asp	Ile	Gln	Asn 3135	
	Asp	Asp	Gly	Ala 3140	Arg	Lys	Pro	Ile	Pro 3145		Asp	Lys	Val	Thr 3150		Asn
10	Lys	Arg	Cys 3155		Arg	Ser	Ala	Arg 3160		Asn	Glu	Ser	Ser 316		Pro	Lys
15	Val	Ala 3170	Glu )	Glu	Ser	Gly	Gly 3175		Lys	Ser	Ala	Lys 3180		Leu	Met	G1n
15,	Asn 3185	Gln	Lys	G1y	Lys	Gly 3190	Glu )	Ala	Gly	Asn	Ser 3195		Ser	Met	Cys	Leu 3200
20	Arg	Ser	Arg	Lys	Thr 3205	Lys	Ser	Gln	Pro	Ala 3210		Ser	Thr	Leu	Glu 3215	
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25	Pro	Lys	Lys 3235		Glu	Asp	Asn	Val 3240		Val	Lys	Lys	Ile 3245		Thr	Arg
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- (ii) MOLECULE TYPE: other nucleic acid
  (A) description: /desc = "synthetic oligonucleotide"
- 45 (xi) SEQUENCE DISCRIPTION: SEQ ID NO: 3:

ACCAGGCGTC TCGTGGGCCA CAT

### PCT/EP99/03451

#### Patent claims

- 1. Use of an oligoribo- or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the protein Ki-67, or of a physiologically acceptable salt thereof, for the preparation of a medicament for destroying proliferating cells.
- 2. Use according to claim 1, characterized in that the nucleotide sequence of the oligoribo- or oligodeoxyribonucleotide is complementary to SEQ ID NO 1.
- 3. Use according to claim 2, characterized in that the nucleotide sequence of the oligoribo- or oligodeoxyribonucleotide is complementary to the section from position 197 to 9962 of SEQ ID NO 1.
- 4. Use according to anyone of claims 1 to 3, characterized in that the oligoribo- or oligodeoxyribonucleotide contains 12 to 66 nucleotides.
- 5. Use according to anyone of claims 1 to 4, characterized in that the oligoribo- or oligodeoxyribonucleotide contains 17 to 46 nucleotides.
- 6. Use according to anyone of claims 1 to 5, characterized in that the oligoribo- or oligodeoxyribonucleotide has the sequence (5'-ACC AGG CGT CTC GTG GGC CAC AT).
- 7. Use according to anyone of claims 1 to 6, characterized in that one or more phosphate groups of the oligoribo- or oligodeoxyribonucleotide are replaced by phosphothioate, methylphosphonate, phosphoramidate, methylene(methylimino) and/or guanidine group(s).

- 8. Use according to anyone of claims 1 to 7, characterized in that the oligoribo- or oligodeoxyribonucleotide has a terminal 3'-3' and/or 5'-5' internucleotide linkage.
- 9. Medicament, characterized by a content of an oligoriboand/or oligodeoxyribonucleotide which is capable of
  hybridizing with the mRNA which codes for the cell cycleassociated protein Ki-67, or of a physiologically
  acceptable salt thereof, in addition to conventional
  carrier substances, auxiliaries and/or additives, wherein
  the amount of oligonucleotide is adjusted such that an
  administration of 0.001 to 100 mg/kg of body weight is
  achieved.
- 10. Use according to anyone of claims 1 to 8 for treatment of tumours, autoimmune diseases, cicatrization, inflammations, allergies, rheumatic diseases and rejection reactions following transplantations.
- 11. Process for the preparation of a medicament for destroying proliferating cells, characterized by the use of oligoriboor oligodeoxyribonucleotides which are capable of hybridizing with the mRNA which codes for the protein Ki67, or of a physiologically acceptable salt thereof.
- 12. Process according to claim 11 for the preparation of a medicament for treatment of tumours, autoimmune diseases, cicatrization, inflammations, allergies, rheumatic diseases or rejection reactions following transplantations.
- 13. Process according to claim 11 or 12, comprising combining of an oligoribo- or oligodeoxyribonucleotide which is capable of hybridizing with the mRNA which codes for the protein Ki-67 with conventional carrier substances, auxiliaries and/or additives.

- 14. Oligoribo- or oligodeoxyribonucleotide, characterized in that it is capable of hybridizing with the mRNA which codes for the protein Ki-67, and that it contains 22 to 46 nucleotides, or a physiologically acceptable salt thereof.
- 15. Oligoribo- or oligodeoxyribonucleotide according to claim 14, characterized in that it contains the sequence (5'-ACC AGG TGA GCC GAG GAC GCC AT).

### Abstract

The invention relates to oligoribo- and oligodeoxyribonucleotides which are suitable for treating pathological conditions accompanied by increased cell proliferation. The oligoribo- and oligodeoxyribonucleotides are characterized in that they are able to hybridise with the mRNA which codes for the cell cycle-associated protein Ki-67.

### Figure 1

Complete nucleotide sequence of the cDNA of the protein Ki-67 and the protein amino acid sequence derived therefrom.

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GAAGTTCAAGATTCTAAGCCTATTCAAAAATCACTGAAGGAAAAGTTTCAGGAAATCT	145	THE	315
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ALOPSOPONTOUTTTACASSISSION COLCUMNOTOUTOOTOTOCOOTAAGTCAACATULA 1	27#	ABANGASTTUTTACASTGGGAAGTTUARACTGASTCTQLGGGAGACTACTGACAGA	1055
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T A 1 2 2 3 4 4 4 8 5 6 8 4 2 3 A 7 9 9 9 0 8	1930 555	TOCHAGGAGGGCCAGGCTETGGAAGACCTAATTGGCTTTAAGAGGTCTTCAGAG	1255
CUSTAGRICUTECAMADAGOCOCTECTTCCAGCAGCALATOTCAGALAGAUUTTCCIAA	2040	COCTOSTRATATISMASCASTSCOTTSTCUMATERIAL COCTOSCANTS  F G H I S E A V A A F F T T R H F C E S	1375
CACCACCACGACAGACAGACCTGCCTTCAAAGACACCCTTCTCTATACCCGACCTCA R G C R V A T C L Q R R V S I E R S Q	21 co 635	TOCTOCHOSAGEAGACACCCCANGALGEACALGEACACCCCCANGACACCCCANGACACCCCCANGACACCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACACCCCCANGACCCCCANGACACCCCANGACACCCCANGACACCCCANGACACACCCCANGACACACAC	1395
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Figure 2

# Structure of sugar- and phosphate-modified oligonucleotides

Action 1

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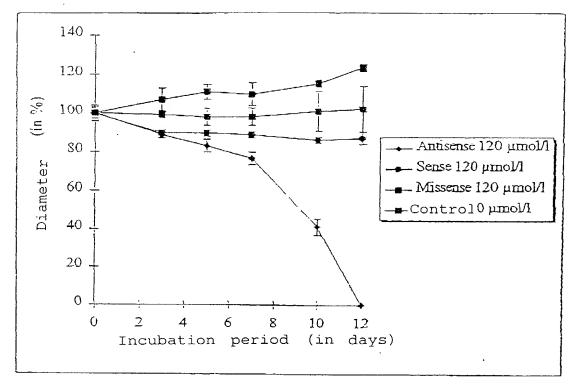


Figure 4

Influence of the solvent on RT4 cells (negative control)

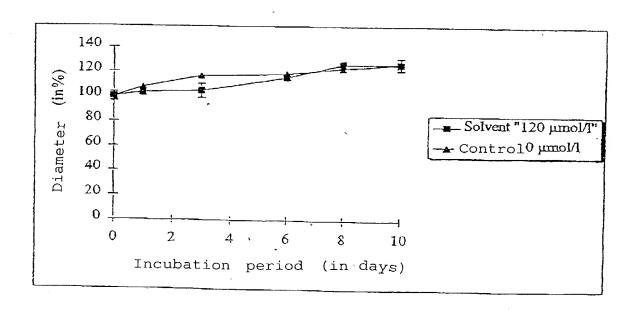


Figure 5

Influence of oligonucleotides on RT4 cells by microinjection

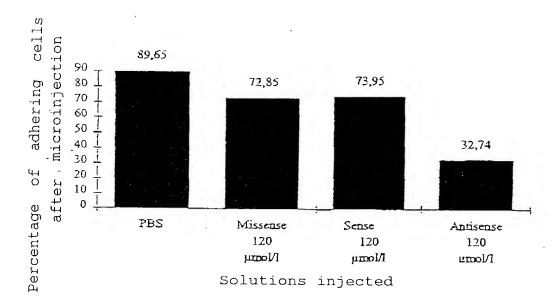
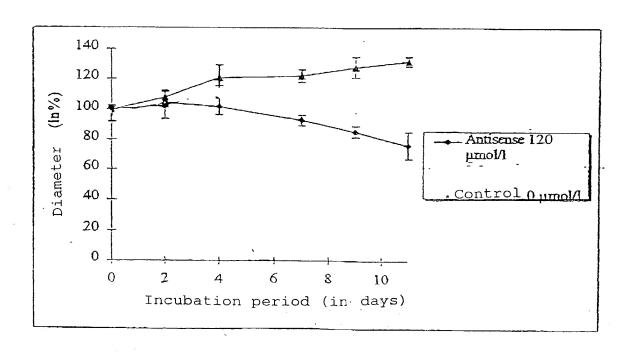


Figure 6
Influence of oligonucleotides on J82 cells



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### DECLARATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[ ] Declaration Submitted with Initial Filing or [X] Declaration Submitted after Initial Filing (surcharge 37 CFR 1.16 (c) required)

As a below named inventor. I hereby declare that my residence, post office address and citizenship are as stated below next to my name. and I believe I am the original, first and sole inventor (if only one name is listed below) of an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITLED "ANTISENSE OLIGONUCLECTIDES FOR TREATING PROLIFERATING CELLS", the specification of which was filed on November 21, 2000 as Attorney Docket No. 661-50303, which is a U.S. National Phase application of PCT International Application No. PCT/EP99/03451.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1,56 including for continuation-in-part application, material information which becomes available between the filing date of the prior application and the national or PCT international filing date of the communion-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(2) -(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international Application which designated at least one country other than the United States of America. listed below and have also identified below, by checking the box, any foreign application for patent or inventor's centificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

viu C	IOR FOREIGN APPLICATION(S)           Inber         Country         Foreign Filing Date (MM/DD/YYYY)           T/EP99/03451         May 20, 1999           3 22 954,2         DE         May 22, 1998	Priority Claimed Yes Yes	Certified Copy Assoched?
tal	steby declare that all statements made herein of my own knowledge are true a believed to be true; and further that these statements were made with the know, punishable by fine or imprisonment, or both, under Section 1001 of Title 18 tements may jeopardize the validity of the application or any patent issued the	of the United States Codereon.	e and that such willful false
n t	treby appoint the registered practitioners represented by Customer No.: 20736 he U.S. Patent and Trademark Office in connection therewith. Directall correspondence of the connection of the con	spondence to 1 at mas 4	anelli, PLLC at Customer
١.	INVENTOR'S SIGNATURE:	20/02/01	Острану 1
	Inventor's Name (typed) Hans-Dieter First Middle Initial	Family Name	Country of Cidzenship
	Residence (City) Barstel (State) (State) German Past Office Address (Include Zip Code) Parkallee 1, D-23845, Barstel Germany		
	- A6)	Date 20/02/0	
	Inventor's Name (typed) Johannes First Middle Initial Residence (City) Feldhorst (State) German	Gerdes Family Name	Country of Citizenship
	Post Office Address (Include Zip Gode) Steinfeld 79 D-71858, Feldbactt, German	<b>Y</b>	
. د	INVENTOR'S SIGNATURE:  Inventor's Name (typed) Andreas	Dare 20/2/6	Germany Country of Citizenship
	First X-Miggle Initial	Family Name	Country of Children in
	Post Office Address (Include Zip Code) Fasanenring 2, D-23627, Groß Gronau. C	ептапу	1 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5
<b>↓</b> .	INVENTOR'S SIGNATURE:	Deinert Family Name	Germany Country of Citizenship
	First Middle Initial Residence (City) Lübeck (State) German	• • • • • • • • • • • • • • • • • • • •	110

Post Office Address (Include Zip Code) Ottemweg 12, D-23560, Lubeck, Germany

#### T49T4557188724 COLLEGATION AND POWER OF ATTORNEY FOR UTILITY OR DESIGN PALENT APPLICATION IN THE UNITED STATES PATEN' AND TRADEMARK OFFICE

and a semiced with initial filling of [X ] Declaration Submitted after Initial Filling (surcharge 37 CFR 1.16 (c) required)

As a below named inventor. I hereby declare that my residence, post office address and citizenship are as stated below next to my name and I believe I am the original. first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plura) names are listed below) of the subject matter which is claimed and for which a patent is sought on the INVENTION ENTITIED. "ANTISENSE OLIGONICLEOTIDES FOR TREATING PROLIFERATING CELLS", the specification of which was filed on November 21, 2010 as Attenday Docket No 661-50303, which is a U.S. National Phase application of PCT International Application No. PCT/EP99/03451.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as arranded by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 including for continuation-in-part application, material information which becomes available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a) -(d) or \$65(b) of any foreign application(s) for patent or inventor's continuate, or 365(a) of any PCT communicational Application which designated at least one country other than the United States of America. listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application baving a filing date before that of the application on which princity is claimed.

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